REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1, 3, 5-11 and 14-18 are in the case.

I. THE ANTICIPATION REJECTION

Claims 1, 3, 5 and 18 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by U.S. Patent 5,268,371 to Mauclaire et al. That rejection is respectfully traversed.

In response, and without conceding to the merit of this rejection, claim 1 has been amended to incorporate the subject matter of claim 2 and claim 2 has been canceled without prejudice. Claim 18 has also been amended to recite the subject matter of claim 2. Claim 13 has also been canceled without prejudice.

Claim 2 does not stand rejected on anticipation grounds over Mauclaire. The Mauclaire structure (I) requires the presence of three pyridyl radicals R^1. The claimed invention now requires four phenyl groups, which is not anticipated by Mauclaire. Withdrawal of the anticipation rejection over Mauclaire is respectfully requested.

II. THE OBVIOUSNESS REJECTIONS

Claims 1 and 3-4, 5-6, 13-15 and 18 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Latouche et al in combination with Mauclaire. In response, and without conceding to the merit of this rejection, claims 1 and 18 have been amended, as noted above, to incorporate the subject matter of claim 2, which is not rejected on obviousness grounds over Latouche in combination with Mauclaire.

Withdrawal of this obviousness rejection on this ground alone is believed to be in order and is respectfully requested.

Moreover, claim 1 of the present application is directed to a compound having a ring structure of Formula VIII representing a porphyrin, chlorin or bacteriochlorin/isobacteriochlorin ring in any of its iminonitrogen tautomeric forms, carrying four m-hydroxy phenyl groups Ar. One or more of the hydroxy groups is in turn linked to an antibody directed against a cell surface antigen of cancer or other diseased cells.

As noted above, claim 1 has been amended to incorporate the subject matter of claim 2, namely to specify that the four aromatic groups are m-hydroxy phenyl groups. This amendment renders the claims novel with respect to Latouche. While Latouche discloses four phenyl substituents around the porphyrin ring, it will be noted that R^1, R^2 and R^3 are all in the ortho or para position on the phenyl ring. In the presently claimed invention, the hydroxy groups are in the meta position. Furthermore, Latouche does not specifically state that the postulated conjugation with antibodies occurs through the carboxy group of R^1, R^2 or R^3,

The Action alleges that it would have been *prima facia* obvious to one of ordinary skill in the art to combine Latouche and Mauclaire. Specifically, the Action states that Mauclaire (column 5, line 40) indicates that the monoclonal antibody can be bound to the porphyrin ring via the R^2 carboxy substituent. Applicants respectfully disagree. The person of ordinary skill reading Latouche would note that the general formula on page 1665 includes four phenyl groups and would also note that those phenyl groups could have one or more —O-CH2-COOH groups attached thereto in the ortho and/or para

positions. The suggestion in the last three sentences on page 1666 to couple the porphyrin ring with monoclonal antibodies is noted. However, the person of ordinary skill man would also note that while Latouche is "presently attempting to link covalently these substituted porphyrms to monoclonal antibodies...", this had apparently not been achieved at the time of the paper. Indeed, no experimental details or procedures are given as to how such covalent linking might be carried out. Latouche does not even suggest that it should be carried out via the carboxy group. Thus, the person of ordinary skill would be left with very little information or guidance as to how monoclonal antibodies are to be linked, and would have no reasonable expectation of success.

Mauclaire does not cure the above-noted deficiencies of Latouche. Mauclaire deals with the problem of linking the monoclonal antibodies by providing only a single phenyl group R^2 around the porphyrin ring, the remaining three R^1 groups being pyridyl radicals. The person of ordinary skill would understand from the Mauclaire reference that to avoid problems of cross-linking antibodies, only a single functional group around the porphyrin ring should be used. The person of ordinary skill would thus be deterred from trying to link antibodies to the Latouche structure which may contain up to eight carboxy groups around the ring rather than the single one taught by Mauclaire.

On the other hand, the starting point of the present invention is porphyrin rings having four m-hydroxy phenyl groups around the ring. This could be expected to lead to problems of cross-linking when coupling to antibodies is attempted. However, the present applicants have proposed a novel experimental protocol (set out in Figure 1) involving activated TFP groups. In this way, it is possible to carefully control the number of monoclonal antibodies linked to the 4-functional porphyrin ring and eventually to

arrive at an antibody conjugate which, as acknowledged by the Examiner, has a higher immunoreactivity than Mauclaire and a better ratio of conjugated antibodies to porphyrin rings.

Therefore, it is surprising that such poly-hydroxy substituted pyridine rings can be effectively mono-substituted with monoclonal antibody, thereby avoiding problems of cross-linking. This is in contrast to Mauclaire which discloses that mono-functional porphyrin rings are required. Thus, Mauclaire states at column 8, lines 10-14:

> *"according to the invention, the choice of tripyridyl derivative of formula (I) makes it possible to avoid any subsequent cross-linking during the coupling of said derivative with a biologically active molecule*

For this further reason, Latouche and Mauclaire lead away from the present invention.

In summary, one of ordinary skill would not have been motivated to rely on the combined disclosures of Latouche and Mauclaire. Even if there had been such reliance (it is believed that this would not have occurred), the person of ordinary skill would have had no motivation to attempt to link monoclonal antibodies to poly-functional pyridine rings such as those taught in Latouche. Absent any such motivation, a *prima facie* case of obviousness has not been generated in this case. Withdrawal of this obviousness rejection is respectfully requested.

Claims 1-3, 5-10,12-13 and 15-18 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 4,992,257 to Bonnet et al in combination with Latouche et al and Mauclaire et al in view of Westermann et al. This rejection is

respectfully traversed.

Bonnett discloses the synthesis of dihydroporphyrins, but otherwise is irrelevant to the presently claimed invention. Bonnett makes no mention of or suggestion of the use of monoclonal antibodies. Mauclaire is not relevant for the reasons discussed above. Westermann describes an old method for coupling porphyrins to a polyethylene glycol (PEG), but there is no disclosure or suggestion of coupling to monoclonal antibodies. The Examiner points to a speculative sentence on page 849, second column, second paragraph, which indicates that this observation represents "an interesting first step in favour of the strategy of conjugating photosensitizing dyes to anti-tumor antibodies". However, this is not a disclosure which would lead one of ordinary skill to the present invention based on the cited art combination. Withdrawal of this obviousness rejection is respectfully requested.

Claim 14 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Mauclaire et al and further in view of WO 92/15683 to Bendig et al. In response, Bendig does nothing other than disclose a particular humanized monoclonal antibody. There is no disclosure or suggestion as to why this particular monoclonal antibody should be employed in the porphyrin rings of the present invention. Withdrawal of this obviousness rejection is respectfully requested

Favorable action on this application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:lfm
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100